TITLE: Mainstream Smoke Constituent Yields and Functional Relationships from a Worldwide Market Sample of Cigarette Brands. Part I: Smoke Constituent Yields at Standard ISO Smoking Conditions.

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ABSTRACT

Conventional cigarette design parameters of tobacco blend, filter construction and ventilation, cigarette paper porosity, cigarette length and diameter, and variations of processed tobacco components lead to a wide array of brand styles with different smoke yields in the market place. When cigarette design is coupled with regional agriculture and growing condition variations, the impact on smoke chemistry can be complex. The objective of this study was to evaluate a benchmarking approach for predicting smoke constituent yields per cigarette for conventional cigarette brands from worldwide markets. Of the brands studied, the majority contained blends of primarily bright, burley, and oriental tobacco. In general, the yields of mainstream smoke constituents determined under standard ISO conditions were well described by weighted linear functional relationships with ISO "tar" ($R^2 > 0.80$ and coefficient p-values < 0.05). These relationships were validated with a subset of brands and greater than 90% of the validation brands smoke chemistry was within the 95% prediction intervals. Those brands with constituent yields beyond the predictive intervals were primarily those with non-blended tobaccos. Regional growing conditions probably contribute to smoke metals yield variation, as seen in the cadmium and mercury yields for two regional brands. The potential impact of carbon in filters on vapor phase smoke constituent yields was addressed with multiple regression. Inclusion of a carbon factor variable improved the functional relationships as evidenced by regression statistics and reduced prediction errors. Functional relationships with reduced prediction errors were established for

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nitrogen oxides and tobacco specific nitrosamine smoke yields by factoring in tobacco filler nitrate or tobacco specific nitrosamine concentrations in the functional relationships. Average differences between measured and predicted yields were generally within the range of one to two measurement standard deviations. Results for ISO smoke yields support the validity of a smoke constituent benchmark approach when brands for which yields are to be predicted have design characteristics within boundaries established by the exploratory brands.

Key Words: mainstream smoke constituents, smoke chemistry, benchmarking approach, prediction intervals, functional relationships

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INTRODUCTION

The tobacco industry has provided cigarette smoke yield "tar," nicotine, and carbon monoxide data for various regulatory agencies for a number of years. More recently, regulations have been adopted or proposed for reporting the yields of specific smoke chemicals found in mainstream or sidestream cigarette smoke **(World Health Organization, 2000a, and International Digest of Health Legislation, 2001).** Cigarette smoke is a complex chemical mixture. Nearly 4000 chemical constituents have been identified in mainstream cigarette smoke **(Dube and Green, 1982, and Roberts, 1988).** These individual chemical compounds and elements, rather than "tar" which is a composite of chemicals, are referred to as smoke constituents. Considerable research has been reported on cigarette smoke constituents identified as harmful or potentially harmful **(IARC 1986 and 1999, Reports of Surgeon General 1989, Hoffmann 1993). Smith et al. (1997, 2000, and 2001)** published comprehensive literature reviews of IARC Group I, 2A, and 2B carcinogens found in mainstream cigarette smoke.

The reporting of individual smoke constituent yields raises a number of issues that remain to be resolved. For example, there are no internationally recognized and supported methods for the generation, collection, and analysis of mainstream or sidestream smoke. For smoke generation and collection, the United States has used the Federal Trade Commission (FTC) Smoke Method for "tar", nicotine and carbon monoxide **(Federal Register, 1967 and 1980).** Internationally, the International Organization of Standardization (ISO) Method is

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typically used to determine cigarette yields **(1999, 2000 a, b and c)**. Both the FTC and ISO standard methods are executed with smoking parameters of 35 mL puff volumes, 60 s puff intervals, and 2 s puff durations. Neither method incorporates smoke constituent analysis guidelines.

Massachusetts **(1997)** and Texas **(1997)** currently require nicotine yield reporting based on smoking machine conditions of 45 mL puff volumes, 2 s puff duration, 30 s puff intervals, and 50% of filter ventilation holes blocked. The Department of Public Health (DPH) of Massachusetts **(Massachusetts, 1998)** also proposed legislation that would require smoke constituent yield data to be determined at this particular smoking condition.

Canadian regulations require reporting smoke constituent yields using both the standard ISO smoking regimen and an intense smoking regimen of 55mL puff volumes, 2 s puff durations, 30 s puff intervals, and total blockage of filter ventilation holes. The Canadian Government has stipulated both machine smoking conditions and smoke constituent analytical methods in its Tobacco Act Reporting Regulation for cigarette products marketed in Canada **(Canada Government Tobacco Act, Schedule 2, 2000).** This is the only known situation where analytical methods are specified within the regulation.

To date, no smoking protocols other than FTC and ISO methods have been validated through interlaboratory studies. A CORESTA Smoke Study Group is currently directing a collaborative study that includes the standard ISO method and two alternative smoking conditions for "tar," nicotine, and carbon monoxide yields **(CORESTA, 2000).** Compared to "tar," nicotine and carbon monoxide,

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considerable differences exist among testing laboratories in their practices in the collection and analysis of smoke constituents. This lack of standardized test guidelines result in data quality (accuracy and precision) varying from laboratory to laboratory. A CORESTA Task Force Special Analytes Group was convened in 1999 with the objective of standardizing methodologies for the determination of smoke constituents through collaborative testing **(CORESTA, 1999)**. To date, this is the only known endeavor in which method standardization is being internationally addressed. Method standardization is a lengthy process requiring multiple laboratory participation. It will be years before the emergence of interlaboratory-validated test methods for all of the smoke constituents. For the time being, reporting smoke constituent yields of trace quantity without standard methods remains a significant challenge. Numerous publications are available that review standard smoking machine testing methods, alternative smoking methods, and the relevancy of any smoking machine testing protocol to smoking and health issues **(World Health Organization, 2000b; Borgerding, 1997; Baker, 2002; National Cancer Institute, 1996 and 2001; Federal Register, 1997).**

Laboratory availability and capacity are other issues to be recognized as requirements for expanding the reporting of smoke constituent yields. Worldwide, there are a limited number of accredited laboratories with the capability and capacity to handle multiple smoke constituent analyses under a variety of smoking conditions for a large number of brands. Future laboratory capacity may develop to meet demand as more regions adopt smoke constituent

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reporting regulations. However, additional testing capacity without standardized methods will likely produce data that cannot be readily compared.

An objective of this study was to demonstrate the predictability of mainstream smoke constituent yields. An alternative to measuring all constituent yields for each brand in a market was to develop functional relationships between the yields of standard cigarette yield parameters and smoke constituents. In this study, relationships were developed from one representative population of cigarette brands and then applied to a test series of brands. Benchmarking encompasses the testing of a set of cigarette brand samples having cigarette design features that are representative of the marketplace. Functional relationships are then established between the yields of each smoke constituent and the predicting variables. The predicting variables are usually the fundamental yield parameters of mainstream smoke "tar," nicotine, or carbon monoxide determined using standardized smoking methods. These functional relationships were subsequently used to predict constituent yields for other brands that were not tested. This study was not the first to demonstrate the potential utility of a benchmarking approach. It was, however, the first study to include brands marketed in a wide distribution of geographical regions and tested at three smoking conditions. Benchmarking offers a technical alternative for providing reliable smoke constituent yield information. This article reports benchmarking results at one standard smoking machine condition. A subsequent publication will include benchmarking with two alternative smoking conditions.

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There are numerous published examples of the use of fundamental yield parameters to predict, compare, or rank other smoke chemistry yields. Several studies included conditions other than FTC or ISO. Young et al. **(1981)** evaluated the adequacy of "tar" for predicting carbon monoxide, hydrogen cyanide, and acrolein. Their conclusion at that time was that "tar" was an inadequate predictor variable for these constituents. In a later study, Rickert et al. **(1983)** compared "tar," nicotine, and carbon monoxide yields of 26 brands, with and without filter ventilation blocking, at several smoking machine conditions. They concluded that the relative ranking of cigarette yields at three smoking conditions (with 100% filter ventilation blocking at the "intense" condition) was essentially maintained and that "tar," nicotine, and carbon monoxide at two alternative smoking conditions could be predicted from yields at standard smoking conditions. Jenkins et al. **(1983)** investigated mainstream smoke yields of "tar," nicotine, carbon monoxide, nitrogen oxides, and hydrogen cyanide at FTC smoking conditions for 32 cigarette brands over a wide "tar" range. They concluded that the smoke yield of the constituents studied could be estimated within 50% if the brand "tar" were known. Chepiga et al. **(2000)** reported mainstream smoke constituent yields for a sampling of 1995 U.S. market cigarette brands and two University of Kentucky reference cigarettes. The analytical work was part of a study to assess smoke chemistry and smoke mutagenicity relationships for commercial brands and reference cigarettes. For all brands tested at FTC smoking conditions, mainstream smoke constituent yields increased with increasing "tar." Linear correlations determined between

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mainstream "tar" and constituent yields were significant. The authors noted that this was particularly relevant because of the wide range of design features of the cigarette brands studied.

An extensive benchmark study was done cooperatively with the Massachusetts DPH by four U.S. tobacco companies in 1999 **(Borgerding et al., 2000).** Mainstream smoke constituent yields of brands representative of the U.S. market were determined at smoking conditions defined by the Massachusetts DPH (MDPH): puff volume, interval, and duration of 45 mL, 30 s, and 2 s, respectively, with filter ventilation 50% blocked. Functional relationships were developed between "tar," nicotine, or carbon monoxide, as measured at either standard FTC or the MDPH smoking conditions, and individual smoke constituent yields determined at MDPH conditions. These relationships could then be used to predict smoke constituent yields for other similarly designed brands.

The Canada Tobacco Act Reporting Regulation allows for use of linear functional relationships between "tar" or nicotine and each of the smoke constituents specified in the regulation **(Canada Government Tobacco Act, Part 3, 2000).** The regulation specifies the minimum number of brands to be tested to establish the relationships and the criteria required to demonstrate statistical validity. Predictive models can be used for smoke chemistry yields at either ISO or the Health Canada alternative smoking condition specified in the regulation.

An important element of the benchmarking approach is that brands for which smoke constituent yields are to be predicted must have design parameters that

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are within the range of the design parameters of the brands selected to represent the market. The study reported here and the particular functional relationships developed are applicable solely to brands of Philip Morris Companies. However, the study approach, and the statistical treatment of data are relevant for others conducting cigarette smoke chemistry research and/or analyzing cigarette products for mainstream smoke constituent yields.

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MATERIALS AND METHODS

Cigarettes

Philip Morris commercial brands from various international market regions were tested. Forty-eight filtered brands were selected to include the majority of cigarette design features and "tar" categories available in those regions. Most brands were blended cigarettes consisting primarily of bright ("Virginia" or flue-cured), burley (air-cured), and oriental tobaccos. Three brands contained primarily bright tobaccos. Nine brands had carbon included in the filter construction. ISO "tar" yields ranged from approximately 1 to 14 mg per cigarette. Brands were sampled at production facilities in late 1999. **Table 1** is a summary of characteristics for cigarette brands included in this study. The study used a split-sample analysis plan. Forty cigarette samples, including 39 commercial brands and a reference cigarette, made up the exploratory sample group. The other 9 commercial brands and a reference cigarette were in the validation sample group. The validation group included a range of "tar" yields and region representation, and was tested after completion of testing of the exploratory group. The exploratory group data were used to develop functional relationships. The validation group data provided independent assessments of the predicting strength of the functional relationships. The University of Kentucky 1R4F reference **(Davis, et al., 1984)** cigarette was included with each sample group for consistency comparisons.

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Mainstream Smoke Collection Methods

The current study was performed at three smoking machine conditions. These were selected because they encompass a standard method and two alternative conditions that are each regulated by at least one government agency. Cigarette samples were conditioned following ISO Standard 3402 **(1999)**. All cigarette samples were smoked using three smoking machine conditions: (1) ISO conditions of 35 mL puff volume, 2 s puff duration, 60 s puff interval; (2) Massachusetts DPH ("MDPH") conditions of 45 mL puff volume, 2 s puff duration, 30 s puff interval, and filter ventilation 50% blocked; and, (3) Health Canada ("HC") conditions of 55 mL puff volume, 2 s puff duration, 30 s puff interval, and filter ventilation 100% blocked. Twenty replicates were analyzed for "tar," nicotine, and carbon monoxide yields. Seven replicates were analyzed for mainstream smoke constituent yields. Only data generated at ISO conditions are reported and discussed in this article.

Mainstream Smoke Constituent and Tobacco Filler Analyses

An ISO/IEC 17025-accredited commercial laboratory was contracted to conduct the machine smoking and constituent analyses. The constituents analyzed for this study were representative of those included in several current or proposed government regulations. The choice of constituents was not intended to imply any hierarchy for smoking and health relevance. Many have been cited as potentially harmful by IARC or other health groups. Analytical methods used by the contracted laboratory were identical to those found in current Health Canada regulations **(Canada Government Tobacco Act, Schedule 2, 2000)**.

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Tobacco filler from each cigarette brand was analyzed for tobacco specific nitrosamines (TSNA) and nitrate. The contract laboratory applied outlier statistics **(ASTM, 1994)** to all smoke constituent yield and filler chemistry data. Smoke constituents analyzed in this study and the respective Health Canada mainstream smoke and whole tobacco analysis methods are found in **Table 2**.

Statistics

A functional relationship is a mathematical equation that establishes a quantitative association between a dependent variable and an independent variable or variables. The relationship allows for predicting the unknown outcome of the dependent variable given known values of one or more independent variables. Regression is used to develop these mathematical functions. A key factor in developing functional relationships for smoke constituents was the selection of representative cigarette brands for the exploratory sample set. These brands and their design features established the boundary conditions for future prediction of yields for other brands. Valid predictions could only be made for brands with design characteristics within the boundary of the exploratory set. Extrapolation beyond these boundaries is misuse of the functional relationships. A second factor in the benchmark approach was selection of the independent variables from which strong functional relationships can be developed. The independent variable or variables should be determined through validated methods, have relatively low standard deviations, and correlate strongly with smoke constituent yields. Mainstream "tar", nicotine, and carbon monoxide yields were therefore suitable independent

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variable candidates for functional relationships. The more precise measurements for these fundamental yield parameters, as evidenced by coefficients of variation, relative to other smoke constituents was another reason to select them as potential independent variables.

Relationships between mainstream smoke "tar", nicotine, and carbon monoxide and individual smoke constituents were investigated using SAS statistical software (Release 8.01, SAS Institute, Cary, NC.) and EXCEL 97 (Microsoft, Redmen, WA.). The coefficients of determination, R^2 and adjusted R^2, together with other diagnostic parameters were used to assess the strength and significance of each functional relationship. These included p-value and F-statistics for regression coefficients and model, regression mean square errors (RMSE), and predicted residual error sum of squares (PRESS) **(Myers, 1990 and Glantz et al., 1990).** Each statistic quantifies different aspects of the regression relationship between independent and dependent variables. The larger the value of R^2 and the lower the values of RMSE and PRESS, the better a particular relationship describes the association between independent and dependent variables and, therefore, the stronger its predictive utility. Linear, quadratic, and multiple regression approaches were considered. Regression with transformed variables was also considered for several smoke constituents when filler chemistry was a key factor in yields. Functional relationships were assessed for their capacity to predict the smoke constituent yields of the validation brand set, as manifested by prediction errors (PE). These are the differences between predicted and measured smoke constituent yields. The

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more representative a functional relationship is of the measured values, the lower the prediction errors.

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RESULTS

Mainstream ISO Smoke Constituent Yields

Average mainstream smoke "tar," nicotine, carbon monoxide and smoke constituent yields for each brand in this study and the 1R4F reference cigarette are found in **Table 3**. The results are grouped by exploratory brand and validation brand sample sets. Several smoke constituent yields, particularly for lower "tar" yield brands, were below the limit of detection (LOD) or limit of quantification (LOQ) established by the contract laboratory. Those constituents and respective LOD's and LOQ's are listed in **Table 4.**

Functional Relationships

Functional relationships for each mainstream smoke constituent were generated by regressing the mean yields of the 39 exploratory brands with the mean yields of "tar," nicotine, and carbon monoxide, as measured at ISO smoking conditions. For the purpose of functional relationship development, analytical limits for LOQ and LOD were used instead of omitting low constituent yield brands from the analyses. It was recognized that using LOD and LOQ could impact the functional relationships with a positive bias in the low yield range. This was deemed more acceptable than having brands with higher yield values impart an even larger influence because brands with yields lower than measurement limits were omitted from the regression analyses. Regression coefficients and diagnostic statistics were compared. There were no substantive differences in linear and quadratic regression statistics. Linear models were therefore selected. Analysis of residuals, however, indicated that many

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constituents failed to meet the criterion for homogeneous and normally distributed variance. Residuals tended to increase with increasing "tar," nicotine, or carbon monoxide yield. In order to correct for the deviation from the basic regression assumptions, the approach of weighted least squares (WLS) was investigated.

Several weighting functions were evaluated. The inverse of constituent variance, (i.e., $1/\sigma^2$), as most commonly used, resulted in predictive intervals that decreased but varied in width over the range of "tar" or carbon monoxide studied. Those brands with constituent yields below LOD or LOQ could not be weighted because of the absence of standard deviations and therefore were eliminated by the WSL approach. Using the inverse of the independent variable, (e.g., 1/tar or 1/CO), as the weighting factor, which was proportional to the constituent variances, was found to stabilize the variances to meet the basic assumption for all of the constituents. This resulted in increased R^2, reduced standard errors and PRESS statistics as compared to the unweighted analysis.

WLS is a modification of standard regression analysis. It is used when a regression model is to be fitted to a data set with non-constant error variance. Once the proper weight (w_i) is determined that can best correct for the unequal distribution of variances, the methodology then determines the regression coefficients (slope and intercept) by minimizing the sum of the squared residual, SS_{res} **(Myers, 1990, Ch 7),**

$$SS_{res} = \sum_{i=1}^{n} w_i (y_i - b - a x_i)^2$$

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where w_i = 1/tar or 1/CO. Data with large error variances will contribute less to the SS_{res} with weighting. The resulting slope and intercept, generally less sensitive to the weighting, are very similar to those from the unweighted analysis. However, the improved regression statistics are reflected primarily in the error variances, confidence and predictive intervals **(Miller et al., 1993 and Mandel, 1991).** WLS generated predictive intervals with non-constant width, expanded at higher yields and contracted toward the low yield region. This was a more realistic representation of the data used to develop the functional relationships in this study. Weighted regression with inverse of regressor weighting was adopted for the development of functional relationships. The regression parameters from WLS are shown in **Table 5**. Regressions were not included for nickel, chromium, selenium, and arsenic since their ISO smoke yields were below the limits of detection or quantification for the majority of brands. The relatively constant smoke pH among brands precluded meaningful application of the benchmark approach. Therefore, smoke pH was not included in the regression. This same trend was seen in other analyses **(Massachusetts DPH, 1999, 2000, 2001).**

Mainstream ISO "tar," nicotine, and carbon monoxide were strongly correlated with each other and with most mainstream constituents, as indicated by R^2 greater than 0.70. There were exceptions, however. ISO fundamental yield parameters were insufficient for describing the yields of nitric oxide, nitrogen oxides, and tobacco specific nitrosamines (NNN, NNK, NAT, and NAB). As will be seen later in this text, tobacco chemistry can be an important variable to consider for these smoke constituents.

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Many mainstream smoke constituents tend to be associated more with either the particulate phase or the vapor phase **(Hoffmann, 1993)**. Nicotine, polycyclic aromatic hydrocarbons, and tobacco specific nitrosamines are examples of constituents primarily in the particulate phase. Lower molecular weight hydrocarbons such benzene, 1,3-butadiene, and toluene are mostly abundant in the vapor phase. Hydrogen cyanide, for example, is associated with both phases. From the statistics in Table 5, ISO "Tar" is a reasonable parameter choice for linear correlations of ISO constituent yields. This choice is based on regression statistics for constituents associated with either the vapor or particulate phase. ISO carbon monoxide would also be appropriate for vapor phase constituents. In general, ISO nicotine demonstrated marginally weaker association, and therefore poorer predictive ability, with vapor and particulate phase constituents. For this study, ISO "tar" was selected as the regressor for functional relationship development and subsequent prediction. It was noted that carbon monoxide had been used to describe the functional relationships for vapor phase constituents in another benchmark study **(Borgerding, 2000)**. It is recognized that others involved with cigarette development, consumer exposure research, or regulatory concerns may have different objectives and that either carbon monoxide or nicotine may be more applicable in describing the yield relationships for smoke constituents.

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To test the reliability of the established linear functional relationships, the measured constituent yields for the nine validation brands were compared with the predicted yields and the 95% predictive intervals. **Table 6** shows the prediction errors (PE) using ISO "tar". The majority (>90%) of constituents in the validation brands were within the 95% predictive intervals. Measured brand average constituent yields outside the predictive intervals are italicized in Table 6. Of the brands noted, two contained primarily bright tobacco blends (V2 and V7). Differences in cigarette smoke composition between all bright and all burley cigarettes have been reported **(Griest and Guirin, 1977)**. It was observed that mainstream smoke yields for phenol, cresols, isoprene, and benzo[a]pyrene were higher for bright cigarettes than for burley cigarettes. Mainstream smoke from all bright cigarettes was reported to be lower in nitrogen oxides and higher in hydrogen cyanide. In addition to tobacco blend differences, there are differences in processed tobacco components in different market regions. Tobaccos from different regions will further be impacted by agricultural practices and growing conditions. For example, the concentration of metals in tobacco, and consequently smoke, is affected mostly by agricultural practices and growing conditions (Stohs et al., 1997, and Smith 1997). Smoke cadmium yield for brand style (V8) in the study was beyond the predictive interval. This could be the result of unusual growing conditions for a particular crop year or years. Tobacco blending over several crop years does tend to mitigate year-to-year differences. One underlying premise of benchmarking is that brands are fairly consistent over time.

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The PE's for each constituent in Table 6 are comparable in magnitude to the standard deviations of measured yields of the validation brands in most of the cases. Exploratory brand average yields, best-fit lines, 95% prediction intervals, and validation group average yields for each smoke constituent are shown in **Figure 1.** To exemplify the inherent variability, one standard deviation error bars are included for several constituents. Charts for nitric oxide, nitrogen oxides, and tobacco specific nitrosamines are excluded from the set because approaches other than simple linear regression were needed to describe these smoke constituents.

Nine brands in the exploratory group contained carbon in their filter construction. It is well known that carbon has the potential to selectively absorb many vapor phase constituents from mainstream smoke **(Baggett and Morie, 1975, and Williamson, et al., 1965).** Carbon monoxide and oxides of nitrogen are generally not affected by carbon. Carbon in filters has no impact on particulate constituent yields. Brands with carbon-containing filters in this study would therefore be expected to influence the functional regression relationships of vapor phase constituents with a bias toward lower predicted yields of non-carbon filter brands. Similarly, some vapor phase constituents would be over-predicted for brands with filters containing carbon. This influence was reflected in both the quality of the regression relationships (regression diagnostic statistics) and prediction interval width. **Figure 2** demonstrates the differences between brands with carbon in filters and those without for benzene yields. The lack of

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carbon influence on particulate phase benzo[a]pyrene yield, for example, is also seen in this figure.

Functional relationship models for vapor phase constituents were consequently expanded to include a factor for the presence of carbon in filters. Multiple regression relationships were developed using tar and a "dummy variable" of 1 or 0 for the presence or absence of carbon, respectively, for the 39 exploratory brands. Again, regressions were weighted with the inverse of tar yield. The results showed general reductions in standard error of the estimate and increases in R^2 for most of the vapor phase constituents. Weighted regression with and without the "dummy" variable are compared in **Table 7.** Use of a dummy variable for filters with carbon does not take into account different filter construction, different weights of carbon in carbon filters, or the surface areas and activities of carbons used in filters for various brands. Multiple regression adds a level of complexity to the relationships and application of those relationships for predicting yields of other brands. The potential impact of carbon filters should be considered in assessing brand constituent yields and predicting relationships for vapor phase constituents. The benchmarking approach should be equally valid if brands with carbon in filters were modeled separately from those without carbon in future studies. **Figure 3** is a comparison between measured smoke yields and linear and multiple regression predicted yields for benzene and acrolein, as examples. With linear regression, there is one predicted yield line. Predicted yields from multiple regression with tar and a carbon filter factor are grouped in two lines. The lower predicted yields are for

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brands with carbon, as the coefficient for the carbon dummy variable is always negative. It is seen that there is less over-prediction (predicted yield higher than observed) for yields below the linear model and less under-prediction (predicted yields less than observed) of yields above the linear model line with multiple regression. The grouping for predicted yields for brands without carbon is higher than predicted yields using linear regression with carbon only. In general, multiple regression with a carbon factor resulted in lower prediction errors for vapor phase constituents of most brands.

Many of the chemical constituents found in smoke are generated during combustion from precursors found in the leaf. For example, phenolic compounds are derived partially from cellulosic materials in leaf, nitrogen compounds are derived partially from proteins in leaf, nitrogen oxides are derived partially from nitrates in leaf, and carbon oxides come from many leaf precursors through combustion **(Baker, 2002)**. The amounts of these constituents found in mainstream smoke depend in part on the amounts of their precursors in the tobacco that is consumed during puffing and the conversion efficiencies of the precursors. Other smoke constituents are largely distilled intact from the tobacco to smoke during the smoking process. Mainstream smoke constituents such as nicotine, metals, and, to some extent, tobacco specific nitrosamines are in this category. The amounts of these constituents found in mainstream smoke depend on their concentrations in the tobacco that is consumed during puffing, and their transfer efficiencies to smoke.

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As noted earlier, two classes of mainstream smoke constituents, the nitrogen oxides and the tobacco specific nitrosamines, were weakly correlated with either ISO "tar," nicotine, or carbon monoxide. Tobacco filler nitrate and tobacco specific nitrosamine concentrations were therefore used to modify functional relationships for predicting the yields of nitrogen oxides and tobacco specific nitrosamines in mainstream smoke. Filler concentrations of nitrate and tobacco specific nitrosamines for each brand style in this study are found in **Table 8.**

For tobacco specific nitrosamines, multiple regression with variables ISO "tar" and tobacco specific nitrosamine concentration in the cigarette was first assessed. The TSNA cigarette concentration was calculated from the dry-weight basis (filler less water content) cigarette tobacco weight and the dry-weight basis concentration of the component in filler. Multiple regression relationships for NNN, NNK, NAT, and NAB were significantly improved over simple linear regression models as evidenced by higher respective R^2's, lower standard errors of estimates, and lower prediction errors for both the exploratory and validation brands. Examination of multiple regression residuals revealed that brands lower in both "tar" yield and filler TSNA concentration tended to be under-predicted. Brands with either higher "tar" yields and lower filler TSNA concentration or brands with lower "tar" yields and higher filler TSNA concentration tended to be over-predicted. For this reason, variable transformations were investigated. Transformed primary and interactive variables, $(\text{tar})^{0.5}$, $(\text{cigarette filler TSNA})^{0.5}$, and $(\text{tar x cigarette filler TNSA})^{0.5}$, were regressed with smoke TSNA yield. The coefficient for the second primary variable, $(\text{cigarette filler TSNA})^{0.5}$, was

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statistically insignificant. The coefficient for the first primary variable, $(tar)^{0.5}$, was considerably less significant than the coefficient for the interactive variable. The final relationship used for prediction was a simple linear regression of smoke TSNA yields with the transformed, interactive variable (tar x cigarette filler TSNA)$^{0.5}$. Residual analysis indicated no violation of basic assumptions. The result was a significant increase in regression quality with higher R^2, lower RMSE, and lower prediction errors for brands at the low and high range of filler TSNA concentration. This simple model also allowed for one-dimensional predictive intervals and simpler visualization. NAB was an exception, however. Differences between multiple and simple regressions with transformed variables were minimal. Of the four tobacco specific nitrosamines analyzed, prediction errors were relatively greater for NAB. **Figure 4** contains transformed variable regression models and prediction intervals for mainstream ISO smoke NNN, NNK, NAT, and NAB. A similar approach was used for regression model development for nitric oxide and nitrogen oxide yields. Prediction model quality between multiple regression using tar and cigarette nitrate concentration and simple linear regression using a transformed interactive term variable, (tar yield x cigarette nitrate concentration)$^{0.5}$ was similar. Prediction models for nitric oxide and nitrogen oxide are found in **Figure 5.** Prediction errors were minimized relative to simple linear regression using only tar as the independent variable. The use of prediction models beyond simple linear regression for TSNA or nitrogen oxides would have less impact if all brands were more similar in filler concentration of nitrate and TSNA. The fact that the current study included

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brands from a wide range of regional markets, and consequently a wide range of concentrations of these tobacco components, warranted different regression model approaches.

To capture the overall impact of the different regression models on prediction errors for the validation brands, an average absolute relative prediction error (ARPE) was calculated for each constituent. This was simply the sum of absolute relative prediction errors for each brand averaged over the nine validation brands. The relative prediction error for a constituent yield in a particular validation brand is the difference in measured and predicted yields divided by the measured yield. The ARPE was then compared to the coefficient of variation, %CV, for each constituent averaged over the nine validation brands. These averaged values are found in **Table 9.** For vapor and particulate phase constituents, prediction errors were generally within two standard deviations of the measured yield. Average ARPE's were therefore approximately two times the respective average %CV. It should be recognized, with smoke constituents measured at the microgram and nanogram levels, that very small differences in predicted and measured yields will result in large ARPE's. For example, the average ARPE for the nine brands for phenol and pyridine were 22% and 21%, respectively. Those percentages would equate to average prediction errors of 2.1 micrograms and 1.8 micrograms. An ARPE of 21% for NNK yields would equate to an average prediction error of 10 nanograms. If the average predicted error for 4-aminobiphenyl were 1.0 nanograms, the ARPE would be 50%.

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DISCUSSION

A benchmarking approach for obtaining reliable cigarette smoke constituent yield information was evaluated with a worldwide sample of commercial brands. The approach was applied to smoke yield data obtained at standard ISO smoking conditions. The results for the diverse range of brands supported the underlying assumption that smoke constituent precursors in tobacco were available somewhat uniformly across tobacco blends from the different regions. Precursors include, for example, tobacco proteins, cellulose and lignin materials, and nitrogen-containing compounds. Mainstream smoke constituent yields increased with smoke "tar," nicotine, or carbon monoxide yields. Smoke "tar" is directly related to tobacco consumed during puffing, which in turn is dependent on cigarette design.

Benchmarking is based on two key elements. Cigarettes for which smoke constituent yield predictions are to be made must have design and tobacco blend characteristics within the boundary established by the benchmarking set of test brands. A subset of this element is brand quality and consistency. This particular study was based on the brands from one manufacturer. Extrapolation to other manufacturer's brands not included in the benchmark would be misuse of the regression relationships. Applying the functional relationship to other manufacturers' brands, i.e., interpolation, could lead to predicted yields with excessive and unknown errors. The second key element for benchmarking is the single-laboratory study design. Since there are currently no universally recognized smoke constituent analyses methods, it was important to use the

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same laboratory and methods for a particular constituent analysis. This lack of standardized test methodology for smoke constituents presents a significant challenge for researchers, manufacturers, and regulators in study design and data interpretation. Laboratories will practice their own methods and comparison of data across laboratories can be difficult. In the near future, the single laboratory approach in which quality controlled and validated methods are used is a viable option for maintaining data consistency. However, the accuracy of the test methods in a single laboratory approach can not be determined in the absence of standardized methods.

The utility of the benchmark approach is determined by how closely predicted yields compare to measured yields. Prediction errors for smoke constituents of the validation brands in this study were moderate when examined relative to other sources of potential variation. One source is the point-in-time variation in a single set of sample replicates, as evidenced by the magnitude of the standard deviation, which is confounded by both cigarette and method variation. A longer-term source of variation is inherent in more subtle day-to-day fluctuations in instrument calibrations, technician performance, and smoking machine operations. Testing laboratories practicing sound quality control procedures will minimize, but not eliminate, these short and long term variations. The long-term variability in method execution was estimated by comparing average constituent yields for the 1R4F Kentucky reference cigarette reported by the contract lab for several company studies **(Table 10)**. Analyses were performed over an 11-month period with the laboratory using the same methods throughout.

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Consistency of the reference cigarette was assumed. Average 95% confidence intervals for standard smoke parameters ("tar," nicotine, puff count, etc.) were approximately +/- 7% of parameter means. For mainstream smoke constituents, the average 95% confidence intervals for the mean yields were considerably wider. Vapor phase and particulate phase constituent average 95% confidence intervals were +/- 18% and 22% of mean yields, respectively. These confidence intervals were of similar magnitude to most of the prediction errors in the current benchmark study.

A second source of variation in smoke constituent yields is the brand itself. As previously noted, natural products such as tobacco are subject to crop year weather variations, regional agricultural practices, and tobacco processing differences. Tobacco blending accomplishes considerable smoothing of tobacco differences, but some variation is still expected. For this reason, a smoke constituent yield measured for a brand produced today could vary somewhat from the yield for the same brand produced at another time. An example of typical smoke constituent yields variation for a single brand produced over a period of time is seen in **Table 11**. The brand was tested monthly over a nine-month period by an internal research laboratory. The measured yield variation included both brand variation and laboratory method variation over time. A significant point of the information in **Table 11** is the magnitude of the 95% confidence intervals around the mean constituent yields. The average 95% confidence interval for all smoke constituents analyzed was +/- 26% of the means for this time period. These intervals are only moderately greater than the

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confidence intervals around the means for the 1R4F reference cigarette tested by the contract laboratory over time. The intervals are also similar in magnitude to the average relative prediction errors for the validation brands in this current benchmark study. These two examples of smoke constituent yield variations support the premise that the predicted yields and prediction intervals, generated from an appropriately designed benchmark study, are valid options for providing smoke constituent yield information for conventional cigarette brands represented in that study design. The 95% prediction intervals generated from the regression functions provide reasonable expectations of the variation for brands at some average "tar," nicotine, or carbon monoxide yield level.

To conduct benchmark studies in a multiple laboratory setting, the impact of the lack of standardized methods is immediately clear. **Purkis, et al. (2001)** compared ISO smoke constituent yields for three brands tested by six laboratories. Each laboratory used its own internally validated methods. All laboratories reported the same relative ranking of constituents yields for the brands but there was significant variation between laboratories for particular constituent yields. Ratios of highest to lowest reported yields ranged from 1.09 ("tar") to 3.20 (quinoline). The authors postulated that, on average, differences greater than 60% between laboratories would be required for confidence that observed yield differences were statistically significant. In contrast, within-laboratory variation for constituent yields was significantly lower with average coefficients of variation of 9%. Data reported in **Table 12** reinforce the conclusions of Purkis. Smoke constituent yields for the 1R4F reference cigarette

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reported by two contract laboratories (point-in-time measurement) and from several literature sources were compared. The ratios of maximum to minimum reported constituent yields ranged from moderate (approximately 1.1) to significant (greater than 2.0). These examples illustrate the need for caution in comparing smoke constituent yield data from different testing sources. Inter-laboratory method standardization is not anticipated in the near future.

A benchmark approach can provide predicted smoke constituent yield information with acceptable prediction errors. A limitation of benchmarking is the inability to reliably predict constituent yields for brands with some unusual characteristic not anticipated from the design range of the model brands. This limitation would be minimized by successively adding new brands to the benchmarking model brands over time and including a validation set of brands as an internal check of the functional relationships. Benchmarking is useful only to the extent that the test brands are representative of brands for which yield predictions are to be made. Prediction errors cannot be eliminated. The magnitudes, however, should be in the range of expected method and brand variation provided the basic tenets of a benchmarking approach are recognized.

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